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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/903,393 | ALLEN, KEITH D. | |
| | Examiner | Art Unit | |
| | Thaian N. Ton | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *36-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



5.00

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/19/05 has been entered.

Applicants' Amendment, filed 7/19/05, has been entered. Claims 1-35 are cancelled; claims 36, 42, 44 and 45 have been amended; claims 36-48 are pending and under current examination.

### *Specification*

The amendment filed 7/19/05 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention.

Applicant has amended the specification at page 10-11, to incorporate US Provisional Application 60/084,194. This reference is not considered new matter because the original specification incorporated USSN 08/971,310 by reference, which was converted to the Provisional Application 60/084194. However, the additional references are considered new matter. The references include a second provisional application (60/084,949), a utility application claiming priority to the two provisional applications (09/193,834) and a second utility application that is a continuation of the first utility application (09/885,816; published as US Patent 6,815,185). There is no evidence that these newly referenced applications were contemplated as being part of the original specification as an incorporation by reference. The reference to "U.S. Patent no. 6,815,185 issued November 9, 2004, which is based on U.S. Patent Application No. 09/885,816, filed June 19, 2001, which is a continuation of U.S. Application No. 09/193,834, filed November 17, 1998,

now abandoned, which claims priority to provisional application no. 60/084,949, filed on May 11, 1998, and provisional application no. 60/084,194, the disclosure of provisional application no. 60/084,194" should be replaced with "US Patent Application No. 08/971,310, which was converted to provisional application no. 60/084194". The other applications should not be included.

## *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 36-48 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. This rejection is maintained for reasons of record advanced in the prior Office action.

Applicants have now amended the claims to recite a transgenic mouse whose genome comprises a null endogenous limulus clotting factor protease-like allele, wherein, in specific embodiments, the mice have a phenotype of increased sensitivity to pain and increased susceptibility to seizure, methods of producing the mice and a method of using the mouse to identify agents capable of modulating the activity of a gene comprising a coding sequence comprising the sequence of SEQ ID NO: 1.

1. *Well Established Utility.* Applicants travelimulus clotting factor protase-like this rejection because they argue that where an invention has a well-established utility or is useful for any particular practical purpose, the invention fulfills this standard. Applicants argue that the present invention has a well-established utility since a person of ordinary skill in the art would immediately appreciate why knockout mice are useful. Applicants argue that the claimed invention has a well-established utility (citing MPEP 's guidelines) if 1) if a person

of ordinary skill in the art would immediately appreciate why the invention is useful based upon the characteristics of the invention, and 2) the utility is specific, substantial and credible. Applicants cite the prior Office action, noting that it would be scientifically well-known to knockout a gene to determine its function, or what will happen when the gene is not expressed. Thus, Applicants argue that it is not debated that a person of ordinary skill in the art would immediately appreciate why the invention is useful for determining gene function. See pp. 5-8 of the Response.

This is not persuasive. As noted in prior Office actions, the claimed knockout mice lack utility for the reasons set forth in the previous Office action. For example, knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. However, the contemplated utilities of using the instant mice to obtain a clue to a pathway is not a considered "substantial utility". This constitutes further research to determine what how a particular gene functions and further research is not considered a well-established utility.

2. *Specific Utility.* Applicants further argue that the invention has specific utility because use of the protease-like -/- mice to study the function of the protease-like gene and the associate of the protease-like gene function is specific to the mouse. Applicants request that the Examiner explain how 1) the asserted utility of determining the function of the protease-like gene would be applicable to all other knockout mice and 2) how the asserted utility of studying the association of the protease-like gene with pain and seizures would be applicable to all other knockout mice. Furthermore, claim 42 recites utilizing a *lacZ* gene, and Applicants argue that expression is inserted into the locus of the protease-like gene, and that expression is driven by the endogenous promoter. Thus, Applicants argue, the expression of *lacZ* indicates where the protease-like gene, and that this use is specific for this particular mouse, and not a general technique. Applicants request

that the Examiner explain how all other knockout mice would be used to study the expression of the lumulus clotting factor protease-like gene. See pp. 8-9 of the Response.

These arguments are not persuasive. A specific utility is that which is specific to the subject matter claimed. Studying gene function is a general utility that would be applicable to any knockout mouse. MPEP §2107.01, which discusses specific utility, provides further support for this. The instant disclosure lacks a correlation between the knockout of the limulus clotting factor protease-like allele and phenotypes that reasonably correlate to the function of this gene. This is analogous to what is stated in the MPEP: "For example, indicating that a compound may be useful in treating unspecified disorders, or a compound that has "useful biological" properties, would not be sufficient to define a specific utility for the compound. Applicants argue that these mice have specific utility because the utilities contemplated are specific to limulus clotting factor C. This is not the case. Utilizing *lacZ* as a marker gene is a general utility and does not define a specific utility for the mouse. Furthermore, the lack of correlation between the phenotype and the function of the limulus clotting factor C, which is a factor in the blood clotting pathway fails to provide utility to the invention. There is no correlation between the observed phenotypes and the knockout of the limulus clotting factor C gene; thus the utility of these mice are not readily apparent.

3. *Substantial Utility.* Applicants argue that the claimed invention has substantial utility, citing MPEP §2107.01 I, and arguing that a use is not substantial if further required to identify any use; that the present application provides knockout mice, which have a well-known use in the study of gene function. Thus, the present invention does not need any further research to establish utility because the mice have a real-world use, as demonstrated by the delivery of the claimed invention to at least one large pharmaceutical company. Applicants state that a Declaration from Robert Driscoll provides evidence that the knockout mice

obtained from Deltagen are used for determining gene function and drug discovery purposes, both uses that are clearly stated in the Applicants. Applicants argue that further research is not required to confirm the utility of the instantly claimed mice because the value of knockout mice in determining gene function is well-established and accepted in the art. Applicants argue that they are claiming the transgenic mouse, and not the protease-like or nucleic acid sequence, and that the Examiner must differentiate between the utility of the transgenic mouse and the utility of the target gene. Applicants argue that because the transgenic mouse can be used in a research setting to further characterize the protease-like gene does not mean that the mouse lacks patentable utility because further characterization of the mouse (involving "basic research") is not necessary to confirm its utility in the studying the protein from the protease-like gene. See pp. 10-11 of the Response.

Applicants' arguments have been considered, but are not found to be persuasive. The Driscoll Declaration, which was submitted on May 19, 2005, has been considered previously (see also, Advisory Action, mailed 6/22/05). The Driscoll Declaration is directed to GAL1R knockout mice, which are not within the scope of the instantly claimed invention, which is directed to limulus clotting factor protease-like gene disruptions. In response to the commercial use of the claimed mouse, this is not dispositive of the lack of a specific and substantial asserted utility in the original specification and does not provide evidence of a well-established use at the time the application was filed. There is no indication in Applicants' response that the mice obtained from Deltagen are used for study of gene function and human therapeutic drug development and the Response does not state that the claimed mouse is being used for any particular purpose. Despite this, as set forth above and in the previous office action, use in study of gene function and human therapeutic drug development for an unspecified disease, are not specific or substantial. Applicant is reminded that the requirements under §101 and §112, 1st para. must be met at the time the application is filed. There is no evidence in the

Applicants' Response that the companies are using the mouse for any use identified in the specification. The discovery of a use meeting these requirements after the application is filed does not satisfy the statutory requirements under either §101 or §112, 1st para. See *In re Kirk*, 153 USPQ 48, 52 (CCPA 1967); *In re Wright*, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993). Thus, Applicants' response does not provide any evidence that the requirements of a specific and substantial use were met at the time of filing. With regard to Applicants' arguments that the claimed invention has substantial utility, these arguments are not persuasive because, as shown in previous Office actions, under §112, 1st paragraph, the phenotypes of mice is not predictive nor is it necessarily correlated to what is observed in humans. Although mice and humans may have many diseases, genes, or physiology in common, the art does not support that this would be predictive of the phenotype that results in the knockout of a mouse's endogenous gene. Finally, it is reiterated that the claimed mice do not have a specific utility, as Applicants are referring to a general utility, to use a knockout mouse to study gene function. Furthermore, this is not found to be a substantial utility, as further experimentation and characterization would be required in order to determine what the phenotypes observed in the knockout mouse relate to the gene that is knocked out.

Applicants disagree with the Examiner's assertion that there is no analogy between the instant invention and a gas chromatograph. Applicants argue that one of the asserted uses of the claimed invention is determination of the specificity of the agent by measuring a physiological response of the animal and comparing the physiological response to a control animal, and Applicants request that the Examiner explain why this is not a tool for analyzing other samples (such as an agonist or agent capable of up-regulation of the gene, etc.). See p. 11 of the Response. Applicants argue that the knockout mice have scientific utility, and thus because it is recognized and accepted by the scientific community, this use should be substantial. See pp. 11-12 of the Response.

In response, a gas chromatograph is a research tool that is highly specific and does not require further study of itself and its uses are to analyze a sample. The instantly claimed mouse is not a "general tool" for analyzing other samples, it only would be used to study the function of a single gene, at the most. Furthermore, scientific utility is not equivalent to patentable utility. The fact that the mice require further research as the determination of a role of a gene does not constitute a patentable utility. See also prior Office actions and "substantial utility" guidelines.

5. *In re Brana.* Applicants argue that the legal principles of *Brana* are applicable to the instant case, because the Board that Applicants' specification failed to disclose a specific disease in which the claimed compounds were useful and the Federal Circuit revelimulus clotting factor protase-liked and held that the mouse tumor model represented a specific disease against which the compounds were effect. Thus, Applicants argue that the instantly claimed mouse and its phenotypes (increased susceptibility to seizure and pain) are sufficient to establish the animal's use as a model for pain and seizure. See pp. 12-14 of the Response.

In response, *Brana* addressed a specific disease, and a model for a specific disease. This is not the instant case with Applicants' invention. The mice of this invention fail to have utility because they exhibit a phenotype that fails to be correlated with the function (or lack thereof) of the limulus clotting factor C, which is a factor in the blood clotting pathway. There is no correlation between the observed phenotypes and the knockout of the limulus clotting factor C gene; thus the specific and substantial utility of these mice are not readily apparent. This is because the mice, although they have asserted phenotypes, there is no guidance with regard to this phenotype and the knockout of the gene of interest.

In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse and cells encompassed by the claims to be credible, specific or substantial.

Claims 36-48 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-48 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record advanced in the prior Office actions.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include:

(1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Applicants' argue that it is "well-known" in the art to compare transgenic mice with controls of the same background, and cite the Burke declaration to show that the mice were, in fact, compared to controls of identical background. The Burke Declaration, which was previously considered in the Advisory Action, mailed 6/22/05, was not persuasive. The Burke declaration does not even show that Gene 387 is the limulus clotting factor protease-like allele of the instant invention. There is no evidence in the Declaration, or the accompany Deltabase printout that the mice were compared to controls of identical backgrounds – the printout states that the mice were compared to age and gender-matched control mice, with no teachings with regard to the background of these control mice.

Applicants argue that the specification does not teach how to make a null allele, that the resultant phenotype is unpredictable. Furthermore, Applicants argue that the disruption of a coding sequence by a positive selection marker, as taught by the specification, will result in null allele, which by definition involves ablation of gene function. Furthermore, Applicants argue that there is no evidence provided by the Examiner that the claimed mouse having a null protease like-allele was not made. Applicants argue that the claims encompass heterozygous and homozygous mice, and the specification clearly sets forth how to make and use these

mice. Heterozygous mice are useful for breeding homozygous mice, gene expression analysis, and phenotypic evaluation. Applicants argue that the phenotypes associated with these mice would be inherent to the mice, and that many of the phenotypes will not be associated with genotype, and therefore, be the same as a wild-type mice. Thus the claimed mice will have "wild-type" phenotypes. Finally, Applicants argue that predicting phenotypes *a priori* must be distinguished from reproducibility of the phenotype of the claimed mouse, and that ablation of the function of a gene is expected to result in the same phenotypic response, and that the Examiner has not provided any support that the mice produced by the methods would not lead to a consistent phenotype.

This is not found to be persuasive. The claimed invention is directed to a limulus clotting factor protease-like knockout mouse. The art of record clearly shows that the phenotype of knockout mice is exceedingly unpredictable (see prior Office actions). The lack of correlation between the resultant phenotype and knockout of the limulus clotting factor protease-like gene fails to provide an enabled use for the claimed mice, as one of skill would not know what to use these mice for. If the claimed mice have "wild-type" phenotypes, one of skill in the art would not know how to use these mice, as they would be the same as wild-type mice. The contemplated uses are for the claimed knockout mice. If one used a wild-type mouse, and a knockout mouse with wild type phenotypes, one could not interpret what any particular result would mean. Even the art cited by Applicants support that the resulting phenotype of any particular genetic disruption is also dependent upon genetic background because they teach that Penk1 (-/-) mice on a C57BL/6 background showed elevated levels of anxiety in the light-dark and startle response tests, whereas DBA/2J-Penk1 (-/-) mice showed elevated levels of anxiety in the zero-maze and social interaction tests. Thus, it is clear from this cited art, that different behavioral effects are observed on different backgrounds

Accordingly, in view of the lack of teachings or guidance provided by the specification with regard to the correlation of the claimed phenotypes and the disruption of the limulus clotting factor protease-like gene, and a particular disease or condition, the lack of teachings or guidance provided by the specification to show that all of the -/- mice would exhibit the claimed phenotypes, and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Claims 36-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". This rejection is maintained for reasons of record advanced in the prior Office action.

Applicants have now amended the claims to recite that the knockout mouse has a null limulus clotting factor protease-like allele. Applicants argue that the specification refers to this sequence as SEQ ID NO: 1 and one skilled in the art would clearly recognize that Applicants invented a mouse having a null protease-like allele. Applicants argue that the cited case law is clearly distinguishable from the present case because they involved DNA sequences which encode certain proteins. In the present case, Applicants argue, they are not claiming a DNA sequence, and that each of these cases (*Fiers v. Revel* and *Amgen v. Chugai*) are not relevant to the claimed invention. Finally, Applicants argue that *Fiddes v. Baird* is not relevant to the claimed invention because in this case, Baird claimed mammalian FGF, although their specification disclosed a single species, bovine pituitary FGF. Finally Applicants argue that *Fiddes* is distinguishable from the

claimed invention because Applicants are not claiming mammalian limulus clotting factor protease-like allele, or even mouse limulus clotting factor protease-like allele, but they are claiming a mouse having a null limulus clotting factor protease-like allele, a single species. Thus, Applicants argue that they have possession of the claimed invention. See p. 20-21 of the Response.

This is not found to be persuasive. The instantly-filed specification defines a gene as any DNA sequence that encodes a particular amino acid sequence and/or any other DNA sequence that hybridizes to the complement of the coding sequences disclosed in the specification. See p. 6, lines 22-27. Thus, the specification has described the nucleotide sequence encoding limulus clotting factor protease-like allele, as set forth by SEQ ID NO: 1. However, the genus of limulus clotting factor protease-like genes encompassed by the claims, including those that hybridize to the complement of this sequence, lack a written description. The instant specification does not describe what other DNA molecules, other than SEQ ID NO: 1, fall into this genus. Therefore, one could not have envisioned the primary structure of other nucleotides encoding the gene. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention.

With the exception of the sequence referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or

attributes possessed by any member of the genus of limulus clotting factor protease-like alleles other than that set forth by SEQ ID NO:1. Therefore, only the limulus clotting factor protease-like gene encompassed by SEQ ID NO:1, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 45 is unclear. The claim recites that the null protease allele comprises a coding sequence comprising the sequence of SEQ ID NO:1. This is unclear because if the allele is null, it cannot comprises a coding sequence. Claims 45-47 depend from claim 45.

The prior rejection of claims 36 and 46 as being indefinite for the recitation fo the phrase "capable of" is withdrawn in view of Applicants' amendments to the claims.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 36-38, 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi [**Scientific American**, 270(3): 34-41(March 1994)] when taken with Genbank accession number AA833210 (available publicly on February 23, 1998).

The claims are directed to a transgenic mouse whose genome comprises a null endogenous limulus clotting factor protease-like allele, wherein the mouse is heterozygous or homozygous, wherein the mouse comprises a gene encoding a selection marker, wherein the selection marker is *neoR*.

Capecchi teaches knockout technology applied to mice, and specifically with respect to the disruption of the *HoxA-3* gene and as the method of producing the same applies to determining the *in vivo* biological function of **any** known gene of interest. For example, Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning of the gene to the manifestation of disease (See page 41, column 2, 2nd full paragraph). Capecchi further discloses the essential components of a targeting vector and including a selectable marker, namely *neoR*, [p. 36 and 38, col. 3, p. 39, col. 1-2], and the steps involved for targeted gene replacement in ES cells as well as in mice (pages 36-39 and diagrams). They teach producing chimeric mice, breeding these mice to black famle mice, and then heterozygous mice are mated to produce homozygous knockout mice. See p. 39, #3-4, top of the page.

Capecchi differs from the claimed invention in that the targeting construct does not contain flanking nucleotide sequences that homologously recombine with the genomic limulus clotting factor protease like-allele. The specification teaches that "limulus clotting factor protease-like gene" refers to a sequence comprising the sequence identified in GenBank Accession Number AA833210. See p. 7, lines 7-9.

Note that the claims have now been amended and recite no phenotype for the claimed mice, thus the combined teachings of Capecchi and the publicly available sequence from GenBank provide the requisite teachings and motivation to arrive at

the claimed invention it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to modify the knockout technology of Capecchi, by use of a targeting vector for disruption of the limulus clotting factor protease like-allele in a mouse ES cell with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as it was an art-recognized goal to determine the physiological role of gene of interest by the generation of a knockout mouse.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi in view of Genbank accession number AA833210, as applied to claim 36-38, 43 and 44 above, and further in view of Le Mouellic *et al.*, [**PNAS**, 87: 4712-4716 (1990)].

The claim further limits the transgenic mouse, wherein the null allele further comprises a *lacZ* gene.

Capecchi and the Genbank Accession number AA833210 are described above. They do not teach that the targeting construct comprises a gene encoding a neomycin resistant gene, and further comprising a *lacZ* gene. However, prior to the time of the claimed invention, Le Mouellic *et al.* disclose methods and constructs for making targeted gene disruptions by insertion of a *lacZ* gene in-frame with the target gene, wherein the construct further contains a neomycin resistance gene under the control of an ES cell-active promoter (see Figure 1, and p. 4713, col. 2, 2nd ¶).

Accordingly, in view of the combined teachings, it would have been obvious for one of skill in the art to use the DNA, as taught by the Genbank Accession number, in a particular construct, as taught by Le Mouellic, to produce knockout mice and cells, with a reasonable expectation of success. One of skill in the art

would have been motivated to make such a construct, because, in light of Le Mouellic *et al.*'s teachings, the skilled artisan would have include a *lacz* gene in-frame with the endogenous gene for the analysis of promoter function, including the analysis of tissue-specific expression. One of skill in the art would have expected a reasonable expectation of success, because only standard molecular biology techniques are required to make the targeting constructs, and the methods of gene targeting of mouse ES cells, are well-known in the art, and developed to the extent that any endogenous gene can be disrupted.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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